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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,003	03/14/2005	Daniel S. Martin	636-C-PCT-US	6708

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,003	MARTIN ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16,21 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-16,21 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **1, 17-20, 22-45 and 50-53** have been cancelled, claims **3-5, 7-8 and 11** have been amended, and no new claims have been added as per the preliminary amendment filed March 14, 2005 . One Information Disclosure Statements (1 IDSs) filed December 10, 2004 has been received and made of record. The drawings filed June 13, 2002 have been reviewed and approved.

Claims **2-16, 21 and 46-49** remain in the case.

The disclosure is objected to because of the following informalities:

Applicant is respectfully requested to update the first paragraph of page one of the disclosure to include all cases including PCT's in the chain of cases related to the instant application including all relevant dates and relevant status information.

Appropriate correction is required.

Claims **2-16, 21 and 46-49** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is very broad because of the exclusive reliance on the generic terms "ATP depleting agents," "pyrimidine-depleting agent," and "an anticancer agent," each of which has not been further defined by any specific chemical structures or structures. In addition the generic term "cancer" covers a vast array of different neoplastic disease conditions with widely varying etiologies and sensitivities to compounds known to have anti-neoplastic activity.

B. The nature of the invention: the invention is directed to a method of causing the death of cancer cells by concomitant administration of three substances which have the effects of i) causing depletion of ATP in cancer cells, ii) causing depletion of pyrimidines from cancer cells, and iii) otherwise attacking the cancer cell life cycle with an anticancer agent, respectively.

C. The state of the prior art in the study of the chemical induction of cell death is not limited to applicant's own work wherein a limited number of chemical substances are shown to be effective in the treatment of a limited number of cancer types. See the PTO-1449 references **#3 and #11** and the PTO-892 references **R, S, T and U**.

D. The level of one of ordinary skill is relatively high, because practice of the instant invention requires an understanding of both medical chemotherapy and associated neoplastic cell biochemistry.

E. The level of predictability in the art is limited by the absence of data to show that the method of inducing neoplastic cell death (necrotic or apoptotic) applies to more than a limited number of neoplastic disease conditions. The various Martin et al. references disclose the effects of several different anti-cancer drugs on mouse breast tumors only. The Geschwind et al. group (PTO-1449 ref. **#3**) has disclosed the efficacy of 3-bromopyruvate against rabbit liver cancer, but this was observed to occur without the presence of the "PMA" combination used by Martin et al. Therefore, the data presently in hand fails to permit the ordinary practitioner to extrapolate to "cancer" in general.

F. The amount of direction provided by the inventor in detail with regard to a limited number of soft tissue neoplastic diseases. However, applicant does not describe how to treat any one of the various pancreatic cancers, liver cancers, bone cancers or brain cancers.

G. The existence of working examples is limited to breast cancer, sarcomas, leukemia and transplanted breast cancers.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be undue because applicant has not limited the instant claims to the specific groups of active ingredients or to the specific neoplastic disease conditions enabled by the disclosure.

Claims **2-16, 21 and 46-49** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

The functional definitions of the components of the pharmaceutically active composition in claims **2, 21 and 46** are directed to a vast number of chemical compounds which have not been described in the instant disclosure in a manner permitting the ordinary practitioner to have the guidance necessary to make or to use a very large proportion of the compound mixtures encompassed by said definitions. Examiner finds at page 38 of the disclosure only 4 combinations of ATP-depleting and other compounds provided in the "Examples" section and none of these compound mixtures defines the subject matter in sufficient detail to permit allowance of claims wherein the individual components of said mixtures are defined generically. Examiner suggests that each of the instant exemplifications be made the basis of a separate claim or set of claims with limitation to the specific neoplastic disease condition(s) enabled by specific embodiments. The generic term "cancer" is also not appropriate in the instant patent claims because the medical treatment of neoplastic disease conditions remains highly unpredictable, particularly in light of the very small number of specific exemplifications of neoplastic disease treatments disclosed herein (applicant has disclosed tests of the instant claimed method on human breast cancer xenografts at pages 23, 29, 39, and 41; a human ovarian cancer xenograft at page 39; and a human pancreatic cancer xenograft at page 39).

Examiner also reminds applicant that *Brenner v. Manson* remains good law (148 USPQ 689 (S. Ct., 1966) at p. 696, column 1) and stands for the proposition that "[A] patent is not a hunting license ... [i]t is not a reward for the search, but compensation for its successful completion."

Examiner expects that applicant may elect to file multiple applications over time as research on the actual scope of the instant claimed invention is being conducted as an ongoing effort, with additional data being added to each application as said data becomes available either directly during drafting or subsequently as a declaration. The accumulation of additional data is critical to establishing the actual scope of the instant invention as envisioned, a topic of repeated, but incompletely enabled, speculation within the instant disclosure. And without said

additional enabling experimental data, allowance of claims of greater scope than that suggested above is unlikely.

Claim **8** is objected to because of the following informalities:

In claim **8** at line 2, the term "agents" is improperly plural.

In claim **2** at line 7, the term "De Novo" is improperly capitalized. See also claims **3, 21** (both occurrences), **48 and 49** (both occurrences) for the same error.

Appropriate correction is required.

Claims **2-16, 21 and 46-49** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim **2** at lines 2-5, the term "at concentrations which deplete the ATP levels to at least 15% of normal in cancer cells" is a method of treating limitation and therefore not properly part of a composition claim. Deletion is respectfully requested. Alternatively the noted term may be replaced by the term -- effective amount -- or the like.

Claim **2** is incomplete because the functional terms at lines 5-7 beginning with the term "mitochondrial" are not further defined as actual chemical species. The noted terms also lack adequately defined metes and bounds and, because of their functional nature said terms are improperly prospective because they read on species not presently known to have the described effects. See also claims **3, 21 and 46** for the same errors. See claim **4** for a similar error involving the functional terms "pyrimidine-depleting agent" and "pyrimidine antagonist."

In claim **2** at line 1, the term "composition comprising an effective amount" together with the content of method of treating claim **46** suggest that the first noted claim may have been more properly drafted to read -- pharmaceutical composition comprising a pharmaceutically effective amount ... [active ingredient(s)] ... in combination with a pharmaceutically acceptable carrier --.

In claim **2** at lines 8-9, the term "other than 6-Mercaptopurine riboside" appears to be a "proviso" and also includes one inappropriate capitalization. Examiner suggests that such

limitations need to be placed at the end of the claim, preferably as a separate paragraph, and identified with the term of art "proviso:" e.g. -- with the proviso that 6-methylmercaptopurine riboside is not one of said inhibitors -- or the like. See also claims **3, 21** (both occurrences), **46, 48 and 49** (both occurrences) for the same error.

In claims **2, 3, 21, 46, 48 and 49** the terms "cancer," "ATP depleting agents," "pyrimidine-depleting agent," and "an anticancer agent" are each lacking adequately defined metes and bounds because there is no claim which defines the particular diseases being referred to by the first generic term, or to the particular chemical identities of the medicinally active compounds encompassed by the last three generic terms.

In claim **3** at line 2, the term "substantially better effect" is indefinite because it is unclear from the remainder of the claim how the metes and bounds of said claim is distinguished from claim **2**. It appears that claim **3** is only a recapitulation of claim **2** in a manner intended to emphasize an effect inherent in claim **2**, and therefore that claim **3** fails to further limit the scope of claim **2** (improperly dependence). Also, the particular "effect" is assumed by examiner to be a medicinal effect, but is not further defined. The absent definition renders the instant claim incomplete. See also claims **21 and 49** for the same error.

In claim **5**, the term "anticancer agent" renders the instant claim incomplete because the particular compounds which so qualify have not been listed. The noted term also lacks adequately defined metes and bounds and, because of its functional nature said term is improperly prospective because it reads on species not presently known to have the described effects. See also claims **6 and 46** for a similar error.

In claim **7** at line 2, examiner suggests that the claim would have improved clarity if the term -- administered -- is inserted in line 2 following the term "is."

Claim **8** is inconsistent with the content of claim **2**. Applicant is referred to the last two lines of claim **2** and line 2 of claim **8**: the former appears to exclude "MMPR" and the latter claim specifically includes the same compound suggesting a lack of proper antecedent basis. Clarification is respectfully requested.

Claim **8** recites the limitation of individual "ATP-depleting agents" in reference to the requirement of "a combination of ATP-depleting agents" in claim **2**. There is insufficient

antecedent basis for the limitation in claim **8** in the noted limitation found in the preamble of parent claim **2**. See also claims **9-11** for the same error. See also claims **12-16** for a very similar error.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **2-16, 21 and 46-49** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***1-8, 20, 22 and 35-47*** of copending Application No. **10/172,346**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the specified active ingredients of the claimed compositions are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims **2-3, 5-9, 21 and 46-49** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Nord et al.** (PTO-1449 ref. **#11**).

Applicant is referred to page 380, Table 3 (explanation at the top of the table) and associated explanatory text.

Claims **2-3. 5-9, 21 and 46-49** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Stolfi et al.** (PTO-1449 ref. **R**).

Applicant is referred to the fourth paragraph of column 1 at page 4075 and the preceding two paragraphs.

For equivalent references see **Colifiori et al.** (PTO-892 ref. **S**) at page 1943, paragraph bridging columns 1 and 2; **Martin et al.** (PTO-892 ref. **T**) in the paragraph bridging pages 656 and 657; and **Koutcher et al.** (PTO-892 ref. **U**) at page 1145, last two paragraphs of the abstract.

Applicant is respectfully requested to supply a PTO-1449 citing all references authored or co-authored by applicants Martin, Bertino and Koutcher directed to the subject matter of the instant claims, which have not already been made of record, and copies thereof.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX

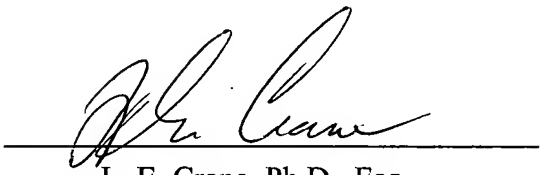
(unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
09/29/2005



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